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Effects of amlodipine and lisinopril on intima-media thickness in previously untreated, elderly hypertensive patients (the ELVERA trial)

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Objective To compare the effects of the calcium channel blocker amlodipine and the angiotensin-converting enzyme inhibitor lisinopril on intima-media thickness (IMT) in elderly, previously untreated hypertensive individuals.

Design A double-blind randomized parallel-group trial (the ELVERA trial).

Patients The study population comprised 166 newly diagnosed hypertensive individuals (aged 60–75 years) with diastolic blood pressure between 95 and 115 mmHg or systolic blood pressure between 160 and 220 mmHg, or both.

Intervention Patients were allocated randomly to groups to receive amlodipine 5–10 mg or lisinopril 10–20 mg for 2 years.

Main outcome measures Before and after 1 and 2 years of treatment, IMT was measured in three carotid and two femoral arterial sites by B-mode ultrasound. The primary endpoint was the change from baseline of the combined mean maximum far wall IMT of carotid and femoral arteries, evaluated by repeated measurement analysis of the treatment effect in an intention-to-treat analysis.

Results After 2 years of treatment, amlodipine decreased IMT by 0.089 mm [95% confidence interval (CI) 0.144 to 0.037]. Lisinopril decreased IMT by 0.065 mm (95% CI 0.124 to 0.010). No differences between the two drugs

were found ($P = 0.18$). Both treatment regimens achieved the greatest reduction of IMT after 1 year, with a slight increase after the second year, whereas the reduction in blood pressure was maintained. Comparing the carotid and femoral arteries, a significant treatment difference in the change from baseline in favour of amlodipine was observed in the IMT of the elastic common carotid artery ($P < 0.05$). The effects of the two drugs on the muscular common femoral artery were not different.

Conclusion In a long-term study, amlodipine and lisinopril reduce IMT to a similar extent in newly diagnosed elderly hypertensive patients. It is suggested that the two drugs have different effects on arteries that are not prone to atherosclerosis. *J Hypertens* 22:1309–1316 © 2004 Lippincott Williams & Wilkins.

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Keywords: intima-media thickness, elderly, hypertension, amlodipine, lisinopril, randomized controlled study

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Introduction

Antihypertensive treatment decreases the incidence of hypertension-related cardiovascular events [1–3]. However, insufficient data are available as to how this treatment affects the cardiovascular damage underlying these events [4], and the clinical effects of antihypertensive treatment on the development of atherosclerosis are also mainly unknown [4]. More trials measuring the effects of antihypertensive drugs on vascular wall characteristics are needed [5].

Increase in intima-media thickness (IMT) is regarded

as an early sign of atherosclerosis [6]. Progression of IMT has been associated with the presence of cardiovascular risk factors such as age, serum low-density lipoprotein cholesterol, hypertension and smoking [7–9], in addition to cardiovascular morbidity [10,11]. Reduction of cardiovascular risk factors reduces IMT progression [12–14]. IMT can be measured with high-resolution B-mode ultrasound, which has been shown to be a validated, sensitive and reproducible non-invasive endpoint assessment of the status of atherosclerosis and prediction of future cardiovascular disease [15].

An important question is whether various antihypertensive drugs affect atherosclerosis to a similar extent. The probability that certain antihypertensive drugs, in particular calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors, exert an anti-atherosclerotic action that is at least partly independent of the blood pressure-decreasing effect is supported by evidence obtained from studies using experimental models of the development of atherosclerosis [16]. This suggests the possibility of differences in effects on IMT in the clinical situation.

The Effects of Amlodipine and Lisinopril on Left Ventricular Mass and Diastolic Function (E/A Ratio) (ELVERA) trial was a prospective, randomized, double-blind, single-centre trial comparing the 2-year treatment effects of amlodipine and lisinopril monotherapy on left ventricular mass in elderly, previously untreated hypertensive individuals. Previously, we found that treatment with amlodipine and lisinopril resulted in equivalent reduction of left ventricular mass in these patients [17]. We now report the findings from the ELVERA trial concerning the effect of both drugs on carotid and femoral arterial wall thickness with respect to detecting clinical differences in vascular remodelling in previously untreated, elderly hypertensive patients.

Methods

Patients

Patients with previously untreated mild to moderate hypertension were enrolled from a population survey performed in the north of the Netherlands in two rural municipalities. Systolic (SBP) and diastolic (DBP) blood pressures were measured with the patient in the sitting position after 5 min of rest. If a difference in blood pressure was detected between the two arms (>5 mmHg for DBP and >10 mmHg for SBP), the arm with the highest blood pressure was used for future measurements; otherwise, the right arm was used. Patients were considered to be hypertensive when four measurements of DBP were between 95 and 115 mmHg or SBP was between 160 and 220 mmHg (or both), derived from several measurements made on three occasions over a period of 4 weeks. Patients with hypertension and aged between 60 and 75 years were selected for the study and advised to restrict their salt intake (low-salt diet). After another period of 4 weeks, blood pressure was measured for the fifth time and hypertensive patients who met the inclusion criteria received placebo treatment for 2 weeks. If blood pressure remained stable during this run-in period, the patients were randomly assigned to the double-blind treatment phase, to receive 5 mg amlodipine or 10 mg lisinopril. After 6 weeks of active treatment the dosage was increased to 10 mg amlodipine and 20 mg lisinopril. Patients who experienced adverse effects with the

higher dose had their dose adjusted to 5 mg amlodipine or 10 mg lisinopril.

Exclusion criteria for the study were: office blood pressure $>220/115$ mmHg; unstable blood pressure after the period of placebo treatment, defined as differences in DBP or SBP readings before placebo treatment of >10 mmHg or >20 mmHg, respectively; secondary hypertension of any aetiology; angina pectoris; manifest coronary artery disease; current or recent history of congestive heart failure; haemodynamically significant valvular heart disease; cardiac arrhythmia; renal insufficiency; insulin-dependent diabetes mellitus. Written informed consent was obtained from all participants and the study was approved by the medical ethics committee of the University Hospital of Groningen. Patient compliance was assessed by counting returned tablets at the various visits.

Blood pressure measurements

Office blood pressure and heart rate were measured with the patient in the sitting position after 5 min of rest twice at every visit (6, 8, 18, 35, 52, 68, 85 and 104 weeks after the start of active treatment) with a 2 min interval between the measurements. In addition, blood pressure and heart rate were measured with the patient in the standing position after another 2 min. The mean of two sitting blood pressure measurements was calculated. SBP and DBP were recorded at Korotkoff phase I and V to the nearest 2 mmHg.

Intima-media thickness measurements

Ultrasound measurements were performed by two experienced and certified sonographers at baseline and after 1 and 2 years of active treatment. An Acuson 128 XP ultrasound system (Acuson Corp., Mountain View, California, USA) with a 7 MHz linear array transducer was used. Three arterial wall segments of both carotid arteries and two segments of both femoral arteries were measured with the patient supine. For the carotid arteries, the far wall segments of the common carotid artery, carotid bulb and internal carotid were imaged from a fixed lateral transducer position. For the femoral arteries, the far wall segments of the common and the superficial femoral arterial walls were imaged from a fixed anterior transducer position. All images were saved on S-VHS tape and analysed off-line throughout the study by an analyst who was unaware of the patients' characteristics.

The primary endpoint of the study was the change in combined mean maximum far wall IMT of 10 segments of the carotid and femoral artery after 2 years of treatment. The combined far wall IMT of the carotid and femoral arteries was taken because atherosclerosis is regarded as a generalized disease. The secondary endpoints were the changes in maximum far wall IMT

of the common carotid artery, a mainly elastic artery, and the common femoral artery, a mainly muscular artery. From studies on repeatability, the error of variation in measurement in the population studied was calculated as 0.03 mm for the primary, combined carotid and femoral far wall IMT, endpoint.

Left ventricular mass measurements

All echocardiographic examinations were performed by one observer, who was blinded to the treatment regimen and blood pressure measurements. An Acuson XP-10 echocardiograph (Acuson Corp.) with a 2.5–4.0 MHz transducer was used. Three measurements were made of end-diastolic left ventricular posterior wall, interventricular septum and left ventricular end-diastolic diameter in two-dimensional mode, according to the Penn Convention. The formula of Devereux and Reichek was used to estimate left ventricular mass [18]. Left ventricular mass was divided by body surface area in order to calculate left ventricular mass index.

Statistical analysis

Monitoring of data, data management and statistical analysis of the results (SAS software package, Cary, North Carolina, USA) were performed by an independent agency (IMRO/Tramarko BV, Berghem, the Netherlands). Results are recorded as mean \pm SD. Analysis of variance was used to test for changes within and differences between treatment groups. To test for changes within and differences between treatment groups after 1 and 2 years of treatment, repeated measurement analysis of variance (RMANOVA) was performed. The outcome variable was the change from baseline IMT. The explanatory variables were treatment and time as categorical main effects, and the interaction treatment \times time to allow for a differing pattern of change in IMT between treatment groups. A correction factor 'statin treatment: yes/no' as categorical variable was implemented. Patients for whom there were valid readings at baseline and at least one valid observation after 1 and 2 years were included in this RMANOVA. In the event of missing values, no imputation was allowed. Results are from intention-to-treat analysis. Statistical tests were two-tailed; the level of significance was set at 5%.

The effects of amlodipine and lisinopril on blood pressure were tested by repeated measurement analysis including all blood pressure measurements after the start of treatment. The percentage of patients whose blood pressure decreased to less than 140/90 mmHg was calculated.

To study the relationship between changes in SBP, DBP and pulse pressure and regression in IMT after 2 years of treatment, linear regression analyses was performed with IMT regression as dependent variable,

and changes in blood pressure, median IMT at baseline and time as independent variables. To study the relationship between changes in left ventricular mass index and regression of carotid and femoral IMT, analyses of covariance were carried out, with change in left ventricular mass index as dependent variable and baseline left ventricular mass index, change in IMT and time as independent variables.

The SD for the IMT was estimated from a repeatability study. The paired absolute differences between the first and the second series of IMT measurements were calculated. The estimation of the SD was based on these differences. The SD for the 'maximum' measurements was 0.34. With 75 patients per treatment group, a between-group difference of 0.06 mm is detectable with a power of 90% for the maximum measurements. This was considered a conservative estimate, because for the final analysis repeated measure analysis was used, including the 1 and 2 years measurements after baseline.

Results

Patients

In the population survey of two rural municipalities, a total of 1969 inhabitants between 60 and 75 years of age had their blood pressure measured. After three serial blood pressure measurements, a total of 386 persons were considered to be previously untreated hypertensive, and advised to take a salt-restricted diet. After a period of 4 weeks of salt restriction, 191 patients fulfilled the inclusion criteria and entered the ELVERA trial. After a 2-week placebo run-in period, 166 patients were allocated randomly to groups to receive amlodipine or lisinopril. Baseline characteristics of these patients are given in Table 1. There were more male patients in the lisinopril group than in the amlodipine group (64% compared with 47%). The two groups did not differ with respect to body mass index (patients

Table 1 Baseline characteristics of 166 patients allocated randomly to the study groups

	Amlodipine (n = 81)	Lisinopril (n = 85)
Age (years)	67 \pm 4	67 \pm 4
Sex (M/F)	38/43	54/31
Body mass index (kg/m ²)	28 \pm 3	28 \pm 4
DBP (mmHg)	92 \pm 8	93 \pm 9
SBP (mmHg)	175 \pm 15	175 \pm 14
Isolated systolic hypertension (n)	44	43
Smokers (%)	42	40
Left ventricular mass (g)	207 \pm 42	224 \pm 55
Total cholesterol (mmol/l)	6.0 \pm 1.0	5.8 \pm 0.9
HDL cholesterol (mmol/l)	1.2 \pm 0.3	1.3 \pm 0.3
LDL cholesterol (mmol/l)	4.0 \pm 0.9	3.9 \pm 0.8
Triglycerides (mmol/l)	1.8 \pm 1.1	1.4 \pm 0.6
Glucose (mmol/l)	4.9 \pm 1.9	4.6 \pm 1.2
Creatinine (μ mol/l)	84 \pm 13	88 \pm 18

Values are mean \pm SD or number. DBP, SBP, diastolic and systolic blood pressures; HDL, LDL, high- and low-density lipoproteins.

were mildly obese), blood pressure, age and lipid profile.

In the amlodipine group, 16 patients had their dose of medication reduced to 5 mg; in the lisinopril group, seven patients had their dose of medication reduced to 10 mg, mainly because of adverse events. Of the 166 patients allocated randomly to the study groups, 120 completed the double-blind treatment phase. Patient compliance judged by mean percentage of tablets taken over 2 years of treatment was $83 \pm 6\%$ for amlodipine and $84 \pm 6\%$ for lisinopril. Reasons for not completing the study in the amlodipine group ($n = 24$) were: adverse events (14), withdrawal of informed consent (six), violation of procedure (two), death (one) and other (one). Reasons for not completing the study in the lisinopril group ($n = 22$) were: adverse events (11), withdrawal of informed consent (four), violation of procedure (four) and other (three).

Blood pressure measurements at baseline and at the end of the study are shown in Table 2. Blood pressure decreased significantly in both treatment groups ($P < 0.0001$), with no differences between the groups. The percentage of patients whose blood pressure de-

creased to less than 140/90 mmHg at the end of the study did not differ between the groups: 26% in the amlodipine group and 25% in the lisinopril group.

Baseline values for the combined mean maximum IMT of the carotid and femoral arteries, and the changes in the first year and the second year compared with the first treatment year are shown in Table 3. After the first year of treatment, there was a statistically significant decrease in IMT in both treatment groups: 0.068 ± 0.097 mm in the amlodipine group and 0.035 ± 0.084 mm in the lisinopril group. During the second year, a slight increase in IMT compared with that at 1 year was found in both treatment groups: 0.032 ± 0.107 mm in the amlodipine group and 0.009 ± 0.107 mm in the lisinopril group (Table 3). A high baseline value was associated with a more marked decrease in IMT. The change in combined IMT from baseline for 'amlodipine minus lisinopril' was -0.024 [95% confidence interval (CI) -0.059 to 0.011 ; $P = 0.18$], indicating no significant differences between the two treatment regimens with respect to changes in IMT.

The maximum far wall IMT of the common carotid artery and the common femoral artery are shown in

Table 2 Blood pressure values at baseline and at the end of study

	<i>n</i>	Mean	SD	Median	Minimum	Maximum
Diastolic blood pressure (mmHg)						
Amlodipine						
Baseline	81	91.7	7.6	93.0	70.0	106.0
End of trial	72	83.3***	6.2	82.0	66.0	100.0
Lisinopril						
Baseline	85	93.0	9.0	94.0	70.0	115.0
End of trial	77	86.5***	8.1	84.0	69.0	111.0
Systolic blood pressure (mmHg)						
Amlodipine						
Baseline	81	174.7	14.7	173.0	131.0	215.0
End of trial	72	148.2***	16.2	148.5	106.0	191.0
Lisinopril						
Baseline	85	174.6	14.1	172.0	140.0	220.0
End of trial	77	148.9***	17.3	147.0	114.0	208.5

***Statistically significant difference compared with baseline ($P < 0.0001$).

Table 3 Combined maximum far wall intima-media thickness of carotid and femoral segments

		Combined maximum intima-media thickness (mm)				
	<i>n</i>	Mean	SD	Median	Minimum	Maximum
Amlodipine						
Baseline	71	1.210	0.281	1.153	0.736	2.224
Year 1	64	1.121***	0.257	1.101	0.733	1.789
Year 2	63	1.166***	0.236	1.163	0.828	1.756
Lisinopril						
Baseline	77	1.194	0.282	1.124	0.795	2.212
Year 1	65	1.116***	0.212	1.091	0.751	1.740
Year 2	63	1.129***	0.232	1.084	0.751	1.698

***Statistically significant difference compared with baseline ($P < 0.0001$). No significant differences between amlodipine and lisinopril were observed ($P = 0.18$).

Table 4. There was a significant treatment difference between amlodipine and lisinopril in the common carotid artery. Amlodipine was associated with a significant reduction in IMT after 1 year of treatment, with a slight increase after the second year of treatment, whereas there was no significant reduction after treatment with lisinopril (Fig. 1). This difference between the two drugs in change from baseline in the common carotid artery was -0.048 mm (95% CI -0.092 to -0.005 mm; $P = 0.03$). In the common femoral artery, both drugs showed a significant decrease in IMT after 1 year of treatment. After 2 years of treatment there was a smaller increase in IMT, without restoration to the baseline value, after lisinopril compared with that produced by amlodipine, but this difference between the drugs (0.023 mm; 95% CI -0.011 to 0.158 mm) was not significant ($P = 0.73$).

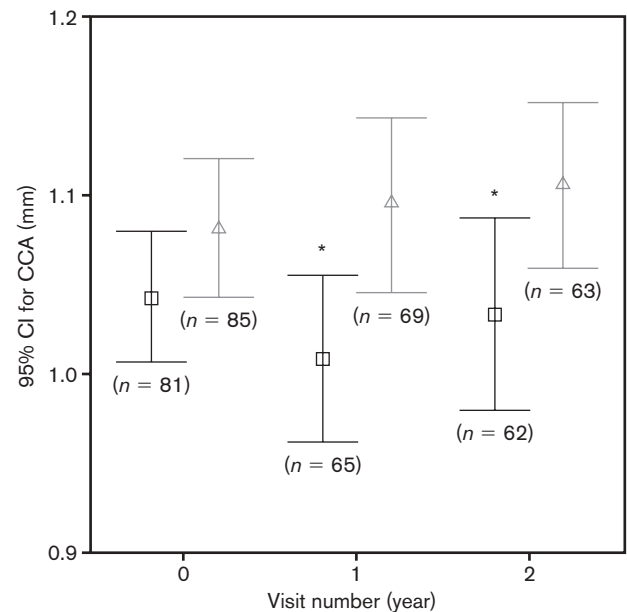
No significant relationships were found between regression in IMT and changes in DBP, SBP and pulse pressure ($R^2 = 0.005$, $P = 0.25$; $R^2 = 0.002$, $P = 0.50$; $R^2 = 0.01$, $P = 0.10$, respectively).

There appeared to be no significant correlation between regression of left ventricular mass index and regression of carotid and femoral IMT ($R^2 = 0.002$, $P = 0.48$; $R^2 = 0.0004$, $P = 0.74$, respectively).

Discussion

In the ELVERA trial, both amlodipine and lisinopril reduced combined carotid and femoral IMT to a similar extent in elderly persons with mild to moderate hypertension. The greatest reduction in IMT in our study was observed after 1 year of treatment. Moreover, the

Fig. 1



Effects of amlodipine (\square) and lisinopril (\triangle) on maximum intima-media thickness of the far wall common carotid artery (CCA). CI, confidence interval. *Statistically significant compared with change from baseline in the lisinopril group ($P < 0.05$).

greatest reduction was found in those arterial segments with the greatest baseline value, as seen in the femoral artery. The reduction in IMT after 1 year was probably mainly a result of the reduction in blood pressure, although a significant relationship between reduction in

Table 4 Far wall maximum intima-media thickness in common carotid artery and common femoral artery

		Intima-media thickness (mm)				
	<i>n</i>	Mean	SD	Median	Minimum	Maximum
Common carotid artery (mm)						
Amlodipine						
Baseline	71	1.019	0.159	1.001	0.647	1.492
Year 1	64	0.971†	0.177	0.945	0.676	1.867
Year 2	63	0.986†	0.199	0.934	0.708	1.940
Lisinopril						
Baseline	77	1.057	0.177	1.023	0.722	1.588
Year 1	65	1.054	0.201	0.982	0.760	1.892
Year 2	63	1.057	0.175	1.029	0.705	1.504
Common femoral artery (mm)						
Amlodipine						
Baseline	68	1.443	0.549	1.337	0.655	2.770
Year 1	63	1.333*	0.639	1.070	0.540	3.177
Year 2	63	1.496	0.616	1.361	0.693	3.050
Lisinopril						
Baseline	72	1.502	0.621	1.370	0.651	3.157
Year 1	62	1.333*	0.632	1.061	0.664	3.648
Year 2	60	1.394	0.631	1.132	0.656	3.030

Statistically significant differences ($P < 0.05$) compared with: *baseline; †lisinopril. In the common femoral artery, no significant differences were found between amlodipine and lisinopril ($P = 0.73$).

blood pressure and decrease in IMT could not be established. It is unlikely that the regression of IMT was the result of regression of the mean, as we used up to 10 measurements of IMT to obtain the maximum IMT as the primary endpoint. Moreover, IMT was not a selection criterion for the study. In addition, the accuracy and reproducibility of dummy images were checked regularly and the reproducibility of IMT measurements was well within the acceptable range [19]. After the first year of treatment, a slight increase in IMT was observed in both treatment arms. It is reasonable to believe that this reflects the effect of ageing, because in placebo-controlled studies the rate of progression of IMT varied between 0.006 and 0.030 mm/year [20,21]. We have previously reported a significant reduction in left ventricular mass after 1 year of treatment, with an even further reduction after the second year of treatment [17]. This discrepancy in increase in IMT and reduction in left ventricular mass after the second year of treatment might explain why we could not find a significant relationship between reduction in IMT and reduction in left ventricular mass.

Comparing carotid and femoral arteries, we found that amlodipine had an effect on the elastic common carotid artery, whereas lisinopril did not. In the muscular femoral artery, both drugs were effective. Although the results suggest a trend that lisinopril has a greater long-term effect on the femoral artery than has amlodipine, the differences were not significant.

The findings of a study by Stanton *et al.* [22] support the observed greater reduction in common carotid IMT after 1 year of treatment by amlodipine compared with lisinopril in 69 previously untreated hypertensive patients. After 1 year of treatment, the mean regression for the common carotid artery was 0.048 mm in the amlodipine group, compared with 0.027 mm in the lisinopril group ($P = 0.04$). In contrast with our monotherapy study, doxazosin and bendrofluazide were added to the treatment regimen if blood pressure remained greater than 140/90 mmHg. When results from all three carotid arterial segments were pooled for the calculations, no significant difference between amlodipine and lisinopril was observed. Therefore, it seems that both drugs have the same effect on atherosclerosis-prone arterial segments, and possibly different effects on segments that are not susceptible to atherosclerosis.

Our findings are also in line with the findings of the Verapamil-Hypertension Atherosclerosis Study, in which the calcium channel blocker verapamil reduced carotid lesions after 4 years of treatment [23]. Similar to our findings, the largest reduction in IMT was seen in arterial walls with the greatest baseline values. Another

study that gives partial support to our findings is the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT), in which the effects of amlodipine on carotid IMT were studied in comparison with placebo in patients with angiographically documented coronary artery disease. Amlodipine significantly reduced carotid IMT, leading to a 0.0126 mm decrease after 3 years of treatment [24]. This reduction in IMT is much smaller than that achieved in our study, but patients in PREVENT were normotensive and the majority were receiving antihypertensive drugs at baseline. There was no treatment difference in the rates of all-cause mortality or major cardiovascular events, although amlodipine use was associated with fewer cases of unstable angina and coronary revascularization. The International Nifedipine Study on Intervention as a Goal in Hypertension Treatment (INSIGHT) study showed that another calcium antagonist, nifedipine, significantly slowed the rate of progression of IMT compared with the diuretic co-amlozide, whereas blood pressure reductions were similar [25]. Another study showed that nifedipine treatment inhibited IMT progression as early as after 26 weeks of treatment in previously untreated hypertensive individuals [26]. Recently, the European Lacidipine Study on Atherosclerosis showed that the calcium antagonist, lacidipine, had a greater efficacy with respect to carotid IMT progression and number of plaques per patient when compared with the β -blocker atenolol after 4 years of treatment [27].

It has been shown that nifedipine improves endothelial function in patients with hypercholesterolaemia, independent of the effect on blood pressure or plasma lipids [28]. This effect of nifedipine is believed to be caused by the enhancement of the bioavailability of endothelial nitric oxide, possibly via an antioxidative protection mechanism [28], which might contribute to the antithrombotic, antiproliferative, and anti-atherosclerotic effects of this dihydropyridine calcium antagonist.

With regard to the effects of ACE inhibitors on IMT, the findings of clinical trials published to date are not conclusive. In the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E, the effects on carotid IMT of 2.5 and 10 mg ramipril compared with placebo were studied in a group of 732 patients, aged 55 years or older, with vascular disease or diabetes and at least one other risk factor [29]. A significant beneficial effect of ramipril on the progression of atherosclerosis was observed after 4.5 years of treatment. The reported progression slope of the mean maximum carotid IMT in the placebo group was 0.0217 ± 0.0027 mm/year, whereas in the 2.5 and 10 mg ramipril groups, progression slopes of 0.0180 ± 0.0026 and 0.0137 ± 0.0024 mm/year, respectively, were observed. Whether or not dose-dependent

ACE inhibition affects IMT remains unresolved. It should be noted that about 33% of patients were treated with lipid-decreasing drugs, equally divided over the three treatment groups. In the Prevention of Atherosclerosis with Ramipril Trial, the effect of ramipril on carotid atherosclerosis was studied in 617 patients with coronary, cerebrovascular or peripheral vascular disease after 4 years of treatment [30]. In this study, blood pressure and left ventricular mass were significantly reduced after 4 years of treatment, but there was no difference between placebo and ramipril in the change in common carotid artery wall thickness and carotid plaque.

One might object that our IMT measurements were not corrected for possible differential effects of the two antihypertensive drugs on changes in diameter in the carotid artery. For several classes of antihypertensive agents, including calcium antagonists and ACE inhibitors, decreases in the carotid diameter have been reported after the start of treatment. Such a decrease in diameter may result in an increase in the IMT and thus might mask a reduction in IMT in the progression of atherosclerosis: in the INSIGHT study, a decrease of 1.2% in carotid lumen diameter was found for nifedipine, which was not significantly different from the 2.5% decrease in the co-amlozide group. For lisinopril and other ACE inhibitors, a comparable decrease in carotid diameters has been reported. Although we cannot exclude small effects of different changes in carotid diameter, it is very unlikely that this would have masked a difference in change in IMT between amlodipine and lisinopril. The relatively small contribution of changes in carotid diameter to changes in IMT has been reported previously [31,32]. Moreover, such effects on carotid diameter occur early after drug initiation (when pressure is reduced) and remain relatively stable without progression as the IMT changes, suggesting that they did not confound IMT progression over time. The fact that similar trends for amlodipine and lisinopril were observed in the IMT over longer periods of time in our study also makes it unlikely that changes in carotid diameter have obscured differences between the effects of the drugs on IMT.

Whether our observed decrease in IMT was the result of functional vasodilatation rather than structural changes remains unclear. Ultrasound imaging cannot discriminate between the intimal layer and the medial layer of the vessel wall in order to distinguish between true atherosclerosis viewed as a disorder restricted to the intimal layer and the adaptive response of the medial layer to changes in tensile stress such as occur during hypertension [33]. However, in contrast to the carotid bifurcation, the common carotid artery is usually relatively unaffected by atherosclerosis [33]. Taking this into consideration, the larger reduction in IMT in

the common carotid artery segment in response to the calcium channel antagonist might suggest an effect on the medial layer as a result of a diminished tensile stress. The reason why amlodipine leads to a greater effect than lisinopril on the carotid artery but not on the femoral artery remains to be explained. The carotid artery is mainly an elastic artery, whereas the femoral artery is mainly a muscular one. This might imply that ACE inhibitors and calcium channel blockers have different effects on elastic and muscular arteries. Conversely, common carotid artery far wall IMT is seen as a marker of arterial wall hypertrophy and not of atherosclerosis, because at this site intrusive plaques are generally absent. In contrast, combined carotid and femoral IMT, in addition to femoral IMT alone, are markers of atherosclerosis because of the high frequency of plaques at these sites. One explanation of the observed differences between the effects of the two drugs on common carotid artery IMT might be a difference in local pulse pressure, as suggested by the findings of a study by Boutouyre *et al.* [34], who hypothesized that the reduction in carotid IMT is mainly the result of a reduction in local pulse pressure. Although the effect of amlodipine and lisinopril on pulse pressure was not different in our study, we did not measure local carotid pulse pressure. The majority of our elderly patients with hypertension had systolic hypertension. The use of calcium channel blockers is favoured in patients with systolic hypertension [35]. Whether the fact that amlodipine, but not lisinopril, produced a reduction in IMT in the common carotid artery may be considered as an advantage of the calcium channel antagonist over an ACE inhibitor in patients with systolic hypertension remains to be investigated.

In conclusion, the calcium channel blocker amlodipine and the ACE inhibitor lisinopril had similar effects on the combined IMT of the carotid and femoral arteries in these previously untreated, elderly patients with hypertension after 2 years of treatment. Different intervention effects of calcium channel antagonists and ACE inhibitors in various parts of the arterial tree were present, with differential effects of treatment on arterial segments that are not susceptible to atherosclerosis. Further studies are needed to clarify the real significance of the observed differences in effects of the two drugs on these latter arterial segments in hypertensive patients.

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